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ROLE OF RICKETTSIAL AND PARARICKETTSIAL  
MICROBES IN THE PATHOLOGY OF PREGNANCY.

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CAJAL M, RAȚIU D, ALEXANDRESCU M M, CUPCEANCU B, in collaboration with  
SURDAN C, POPESCU-DANESCU G, ANAGNOSTE B, ȘORCOC G.

ROLE OF RICKETTSIAL AND PARARICKETTSIAL MICROBES IN THE  
PATHOLOGY OF PREGNANCY.

I. Investigations into the relationship between rickettsial  
and pararickettsial infections of the mother and stillbirth.

Communication presented on the 16 July, 1962, session of the Institute  
of Inframicrobiology, Academy of the Romanian People's Republic.

/This is a translation of an article written in the Romanian lan -  
guage and published in Studii și cercetări de inframicrobiologie  
(Studies and Research in Inframicrobiology), 1962, Bucharest, vol. 13:  
pages 657 -665/.

During the last years in many countries of the globe, world statis-  
tics show an alarming increase in stillbirth.

The causes brought up in classical works, i.e., neuroendocrine imbal-  
ance of pregnant women, placental circulatory disturbances, vascular insuf-  
ficiency of the placenta, various microbic lesions of the placenta, traumas  
of the pregnant, are results rather than causes. Luetic infection, tubercu-  
losis, malaria, which were frequent causes of stillbirth in the past, were  
eliminated to a large extent, although this did not help to reduce the per-  
centage of stillborn children.

Combined with the fact that on the one hand stillborn children are  
also most often immature in physical development, and on the other hand the  
incidence of vascular lesions in the placenta (the probable result of some  
infections which hitherto remained obscure) has increased, these data stim-  
ulated us to undertake investigations in the direction of a possible ricket-  
tsial or pararickettsial etiology.

The investigations of GIROUD and coworkers (8;9;10;11) and of NICOLAU  
and coworkers (12;13;14;15;16;17) into the rickettsial or pararickettsial  
etiology of certain cardiovascular affections opened new promising roads  
for us in the research and interpretation of many pathological phenomena

whose causality has not been hitherto elucidated.

The pathogenetic details of rickettsial or pararickettsial infections, the trend toward latency of the infectious process, the vasotropism and toxigenic activity of the germs are important pathogenetic potentials which can reach any part of the organism. The latent evolution of rickettsial and/or pararickettsial infections is conditioning important immunological reorganizations in the infected organisms among which premonition and allergic hypersensitization are of extraordinary importance in the pathological process of these infections.

The abortigenous nature of rickettsial and pararickettsial infections is generally recognized in animal pathology. Enzoo-epizootic abortions of bovine, caprine, ovine and other species of animals are produced not only by major rickettsias, among which the most frequent is the one due to Rickettsia burneti, but also especially by pararickettsial microbes which are very closely related to microorganisms in the psittacosis-ornithosis-lymphogranulomatosis group.

In addition to abortions, constant premature calvings, congenital weakness, important deficiencies in fetal development, tendency to postnatal pneumo-enteric affections are recorded in contaminated herds which result in a large mortality rate.

GIROUD(8) determined the relation which in several places of France exists between abortions of women and abortigenous ailments of bovines. By serologically examining 87 women who aborted between the second and seventh month of pregnancy, or gave birth to immature non-viable children, he found that 27 women had antibodies for neorickettsias, three had antibodies for R. conori, and three had them for R. burneti. From the fetal membranes the author isolated six strains of rickettsial inframicrobes. By serologically examining one hundred Parisian women who had spontaneous abortions, the same author(7) found six positive cases for R. conori, three for R. burneti, and 25 for Neorickettsia. In another serological study of 263 women who aborted, GIROUD and CAPONI(11) found that eleven were positive for R. burneti, twelve for R. conori, and 27 for Neorickettsia.

While following up 261 women who had had spontaneous abortion in their anamnesis, VOGT and coworkers found that in 115 women who again became pregnant 72 aborted, ten gave birth to dead children, 14 gave birth to viable children who died in the perinatal period, and only ten children were born viable. Among the 261 women surveyed, 44 showed positive serological reactions for Neorickettsia.

The quoted data are the reason of our proposal to investigate the relationship between rickettsial and pararickettsial infections (apparent or latent from a clinical point of view) in the mother and the rate of stillbirth, immaturity, and congenital malformations.

In the present paper we give our results obtained on the relationship between rickettsial or pararickettsial infections and the stillbirth rate.

## MATERIAL AND METHOD.

For investigation we selected 14 mothers admitted to the "Polizu" Maternity whose pregnancy was interrupted after the VI. month, or who delivered dead children at term, without their being able to determine its cause.

The dead children, placenta, and fetal membranes were pathological-anatomically examined at the pathological anatomical laboratory of the "Polizu" Hospital (Dr. F. PASQU). Blood was collected from the mothers immediately after the expulsion of dead children. The obtained serum was examined for the presence of antirickettsial or antipararickettsial antibodies by the microagglutination slide reaction according to the GIROUD method. Rickettsial antigens (provaški, mooseri, conori, and burneti) and the Q<sub>18</sub>\* neorickettsial antigen was put at our disposal by Prof. P. GIROUD of the Pasteur Institute of Paris.

/\*FOOTNOTE: The Q<sub>18</sub> neorickettsial antigen, prepared from a viral strain of ewes, is a group antigen. The term Neorickettsia given by GIROUD to this group of inframicrobes is identical with the term Pararickettsia which we use in this work/.

For the trial isolation of inframicrobic agents, in some cases we used triturated placenta suspended in isotonic NaCl solution and bacteriologically sterilized with tirothrycin and streptomycin. After free sedimentation at +4°C, 0.2 ml of the supernatant fluid was inoculated into the vitelline sac of 7-day old hatched eggs, and 4-6 drops intranasally--under general anesthesia-- into young white mice.

On these biological media many blind passages were made; the eggs and white mice were sacrificed 5 to 7 days after inoculation. For the demonstration of elementary bodies, we used the staining methods of MACHIAVELLO and GIEMSA.

By the same method, we examined serologically 14 mothers who delivered normal children at term and who were used as controls.

## RESULTS.

The result of serological examinations is displayed in Table I. It is seen that in the 14 women whose pregnancies were interrupted in their evolution and who had stillbirth, eleven (=78.57%) has serologically positive reaction for rickettsial and pararickettsial antigens. Among these, three had microagglutinins for R. burneti, one for R. conori, one for Pararickettsia, three for R. burneti and Pararickettsia, one for R. burneti and R. conori, and one for R. burneti, R. mooseri and R. conori.

In the group of 14 control women who gave birth to normal children at term, five (= 35.71 percent) had serologically positive and/or doubtful reactions for the rickettsial and pararickettsial antigens. Among these, two had antibodies for Pararickettsia, one for R. mooseri, one for R. burneti and Pararickettsia, and another for R. mooseri and R. conori.

For the control group the intensity of serological microagglutination reactions is lower than for the group of women who had spontaneous interruption of pregnancy and stillbirth.

TABLE I. Result of serological examinations for rickettsias and pararickettsias in women with stillbirth, compared with women who gave birth to normal children at term.

No.	Numele casului examinat	Motivul pentru care a fost efectuat cazul	Rezultatul rezultatelor de serologie: Jutroare față de anticorale									
			R. propositi	R. maderi	R. ceteri	R. birnii	R. birnii	R. birnii	R. birnii	R. birnii	R. birnii	R. birnii
			1/100	1/200	1/400	1/800	1/1600	1/3200	1/6400	1/12800	1/25600	1/51200
Femei care au născut copii morți												
1	R. G.	Năște la termen copil mort	-	-	-	-	-	-	-	-	-	-
2	R. EL.	Sarcină oprită în evoluție în luna a VI-a. Naște un fat mort	-	-	-	-	-	-	-	-	-	-
3	D. EL.	Năște la termen un copil mort	-	-	-	-	-	-	-	-	-	-
4	Ch. Ec.	Năște la termen un copil mort	-	-	-	-	-	-	-	-	-	-
5	Mn. L.	Năște la termen. Copilul moare după 8 ore	-	-	-	-	-	-	-	-	-	-
6	D. Ag.	Sarcină oprită în evoluție în luna a VII-a. Copil mort	-	-	-	-	-	-	-	-	-	-
7	T. I.	Avort spontan luna a VI-a	-	-	-	-	-	-	-	-	-	-
8	C. EL.	Sarcină oprită în evoluție în luna a VII-a. Copil mort	-	-	-	-	-	-	-	-	-	-
9	S. L.	Sarcină oprită în evoluție în luna a IV-a	-	-	-	-	-	-	-	-	-	-
10	Bl. GL.	Năște la termen un copil mort	-	-	-	-	-	-	-	-	-	-
11	G. G.	Năște la termen un copil nevital. Anterior 3 avorturi spontane	-	-	-	-	-	-	-	-	-	-
12	R. Gh.	Năște la termen un copil mort macerat	-	-	-	-	-	-	-	-	-	-
13	B. AL.	Năște la termen un copil mort	-	-	-	-	-	-	-	-	-	-
14	Mr. L.	Năște la termen. Copilul moare după 8 ore	-	-	-	-	-	-	-	-	-	-
Femei care au născut la termen copii normali												
1	W. EL.	Năște la termen copil normal	-	-	-	-	-	-	-	-	-	-
2	L. Vg.	Idem	-	-	-	-	-	-	-	-	-	-
3	T.	Idem	-	-	-	-	-	-	-	-	-	-
4	M. EL.	Idem	-	-	-	-	-	-	-	-	-	-
5	W.	Idem	-	-	-	-	-	-	-	-	-	-
6	D. C/m	Idem	-	-	-	-	-	-	-	-	-	-
7	P. EL.	Idem	-	-	-	-	-	-	-	-	-	-
8	S.	Idem	-	-	-	-	-	-	-	-	-	-
9	P. AL.	Idem	-	-	-	-	-	-	-	-	-	-
10	M.	Idem	-	-	-	-	-	-	-	-	-	-
11	P. EL.	Idem	-	-	-	-	-	-	-	-	-	-
12	S. Ver.	Idem	-	-	-	-	-	-	-	-	-	-
13	L. PL.	Idem	-	-	-	-	-	-	-	-	-	-
14	R. M.	Idem	-	-	-	-	-	-	-	-	-	-

(See legend next page)

(LEGEND TO TABLE I:)

- a...order number
- b...Name of examined women
- c...Reason for examination of women
- d...The result of microagglutination reactions for antigens ...
- e...Women with stillborn children.
- f...Controls. Women who gave birth to normal children at term.

Text under "e".(Column e)

- 1...At term she delivers a dead child.
- 2...Pregnancy ceased to develop in the VI.month.Delivers a dead fetus.
- 3...and 4...Delivers a dead child at term.
- 5...Delivers at term. The child dies 8 hours later.
- 6...Pregnancy ceased to develop further in the VII.month. Dead child.
- 7... Spontaneous abortion in VI.month.
- 8...Pregnancy ceased to develop in VII.month.Dead child.
- 9...Pregnancy ceased to develop in IV.month.Dead child.
- 10...Delivers a dead child at term.
- 11...Delivers a non-viable child. Previously 3 spontaneous abortions.
- 12...Delivers a dead macerated child at term.
- 13...Delivers a dead child at term.
- 14...Delivers at term. The child dies 8 hours later.

Text under "f"(Group of controls)

- 1 to 14...Delivers a normal child,at term.

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(Text cont.from p.3)

From the placenta collected from Case No.8(C.Fl.) and from the suspension of organs of a stillborn child at the end of gestation(Case No. 12,R.Gh) we were able to isolate two strains of inframicrobes, in the first case both on hatched eggs and on white mice, and in the second case only on white mice.

Both strains are made up of inframicrobic germs of large size(200-250 millimicrons) which could be stained with the method of MACHIAVELLO and GIEMSA, and were visible with ordinary microscopy. In the first five passages made until now, the two strains produced sporadic mortality both of the white mice and of the hatched eggs. The white mice killed 5-7 days after inoculation show foci of lobular pneumonia on whose smears, stained with MACHIAVELLO's or GIEMSA's method, corpuscular formations of rickettsial shape could be demonstrated.

Adaptation of the inframicrobic strains to white mice, or to hatched egg, and identifying examinations are in progress.



## DISCUSSIONS.

In the studies which we made on fourteen women who had spontaneous interruption of pregnancy and delivered dead children we obtained results that confirm those found by GIRAUD. The rate of serologically positive reactions for rickettsias and pararickettsias which we found was 78.57 per cent., compared with 34 to 38 per cent. recorded by GIRAUD(7;11). We emphasize that the majority of women whom we examined came from a rural environment, while those examined by GIRAUD originated from an urban environment.

For the women who in the second half of their gestation period delivered dead or non-viable children(78.57%), the rate of serologically positive cases for rickettsias or pararickettsias which we found is very close to the one published by NICOLAU and coworkers(18) in cardiovascular diseases( 79.81 %). In the group of controls consisting of women who delivered normal children at term, the rate of serologically positive or doubtful cases is 35.71%, while in healthy people of different age groups the percentage published by NICOLAU and coworkers(18) is 28.34%.

The close concordance of the rates of serologically positive cases which we and NICOLAU and his coworkers found raises an important problem in the epidemiology of rickettsias and pararickettsias in our country.

A fact worth pointing out is also that in our investigations we found an increased incidence in serological reactions for Rickettsia burneti and Pararickettsia, just as NICOLAU and coworkers(18) found it in cardiovascular affections.

The clear material evidences gathered by GIRAUD(8;9;10;11), by NICOLAU and coworkers(12;13;14;15;16;17;18), and by other investigators on the rickettsial or pararickettsial etiologies of certain cardiovascular ailments are also very important factors in explicating various etiological aspects in the pathology of pregnancy. If in the course of both flourishing rickettsial infections, and latent asymptomatic infections any portion of the circulatory apparatus were implicated, we should assume that the placental circulatory system was the first to become affected. When dealing either with direct inframicrobic presence and multiplication in the placenta, in the fetal membranes or in the fetus itself, or, indirectly, with inframicrobic toxins acting upon a terrain sensitized beforehand, the disturbance in the neurotrophic exchanges between mother and fetus can be explained.

The results obtained by GIRAUD and coworkers(2;3;4;5;6) in pregnant female rat white rats, experimentally infected with R. prowazeki, neorickettsias, or Toxoplasma gondii justify this hypothesis thoroughly. The epizootology and pathogenesis of abortigenous rickettsias and pararickettsias in animals also furnish us with factors of extreme importance which make us admit that these inframicrobes also operate in the pathology of human pregnancy.

The investigations of SARATEANU and coworkers(19;20;21;22;23;24;25; 26;27) and those of SURDAN and coworkers (29;30;31) on the incidence of pararickettsial infections in different species of mammals and birds, and those of SARATEANU and coworkers on the incidence of pararickettsial anti-

bodies in different groups of workers engaged in animal husbandry, as well as those of NICOLAU and coworkers(12;13;14;15;16;17;18) in the field of rickettsial or pararickettsial etiology of certain cardiovascular affections yield us epidemiological data which are extremely important for our country.

These data may be the point of departure for numerous investigations which could lead to the explication of certain pathological phenomena hitherto still unexplained from an etiological point of view.

Since in the anamneses of the examined women we find in our cases that during pregnancies they had febrile conditions, sometimes with pulmonary repercussions, we believe that latent infections with the incriminated germs could become manifest during an intercurrent pregnancy.

Such small infectious flare-ups, just as other latent, well-known attacks in the group of inframicrobioses, could result in vascular changes in the placenta, and consequently in spontaneous abortion, or in death of the fetus.

Of course, once the etiology of these affections is established, specific preventive therapeutic measures will not wait long to contribute to the resolving of these important public health problems.

In the Czechoslovakian Socialist Republic, CECI and coworkers(1) made experimental research on protecting pregnant women who show serologically positive reactions to ornithotic antigen. While 44 women who previously had 114 pregnancies delivered only 9 viable children, 25 women who were treated preventively with aureomycin in the first half of their pregnancy delivered 24 normal children.

The results of our investigations, expressed by a growing incidence of serologically positive reactions for rickettsias and pararickettsias in women who had spontaneous interruption of pregnancy and deliveries of dead or non-viable children, as well as the fact that from the placenta or from the organs of stillborn children two strains of inframicrobes were isolated with morphological characteristics resembling rickettsiae or pararickettsiae— these results make it possible for us to suppose a rickettsial or pararickettsial etiology in these cases.

#### CONCLUSIONS.

1. In 14 women who had spontaneous interruptions of pregnancy and who gave birth to dead or non-viable children, eleven (or 78.57%) are serologically positive in the microagglutination reaction for rickettsiae and pararickettsiae.

2. In the control group of 14 women who gave birth to normal children at term, five (or 35.71%) had serologically positive or doubtful reactions for rickettsias or pararickettsias.

3. From the placenta of a woman who had a spontaneous interruption of pregnancy, and from the organs of an immature stillborn child we isolated two strains of inframicrobes which show morphobiological characteristics resembling those of rickettsias and pararickettsias.

4. The results of the performed examinations allow us to consider that certain cases of spontaneous interruption of pregnancy and of still-

birth are caused by latent infection with rickettsiae or pararickettsiae.

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and the Institute of Inframicro-  
biology, of the Academy of the  
Romanian People's Republic.

(Russian and English summaries; here omitted)

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